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EXAMINER

WESSENDORF, TERESA D

ART UNIT PAPER NUMBER

1627

DATE MAILED: 10/02/2002

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/782,004

Applicant(s)

DAHIYAT ET AL.

Examiner

T. D. Wessendorf

Art Unit

1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 20 September 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12-25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 12-25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

Art Unit: 1627

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-9, drawn to a method of generating a secondary library and composition, classified in class 435, subclass 4+.
- II. Claims 10-11, drawn to a method using computer, classified in class 70, subclass 19.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are drawn to different methods utilizing different components in the method.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, and the search

Art Unit: 1627

required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

In the telephonic interview of August 19, 2002, applicants elected Group I, claims 1-9 but indicated that a new set of claims would be submitted. (See the Fax Amendment and Response of 9/20/02).

Applicants' election without traverse of Group I, claims 1-9, in Paper No.15 is acknowledged.

The amendments of 9/20/02 (paper 15) cancelled claims 1-11 and presented new claims 12-25.

Status of Claims

Claims 12-25 are pending in the application.

Specification

The disclosure is objected to because:

A). It contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

See e.g., page 12, line 22 and line 24. Applicants are requested to check for other hyperlinks embedded in the specification since they are too numerous to mention specifically.

Art Unit: 1627

B). The attempt to incorporate subject matter into this application by reference to J. Mol. Biol., page 13, lines 1-2 is improper because this is a publication. Applicants are requested to check for other incorporation of material referencing publications since they are too numerous to mention specifically.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

C). The status of SN. 09/127,926 recited at page 16, line 29 has not been provided.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors (e.g., spelling, grammar etc.). Applicants' cooperation is

Art Unit: 1627

requested in correcting any errors of which applicants may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the enzymes protein design using specific program design, does not reasonably provide enablement for any type of secondary library of scaffold protein variants or sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of enabling disclosure is not commensurate with the scope provided in the specification. The specification,

Art Unit: 1627

specifically the Examples, disclose a method for generating secondary sequences of specific enzymes utilizing PDA, not a force field calculation or an alignment program as claimed. The rest of the specification discloses nothing more than general description of the claimed method. It is not readily apparent from the disclosure how the probability distribution table of amino acid residues is generated using only the force field calculation. This is made more complex since the single working example, supposedly a guide to the practice of the broad claimed invention, does not use either a force field calculation or an alignment program. While the enabling disclosure is not limited to the working example however, in an unpredictable art such as protein, one cannot predict the outcome of a specific protein secondary structure to the vast secondary structure of even a single protein. As a skilled in the art appreciates, to date there are too numerous obstacles for the design of even a single secondary structure of a protein, let alone, all or any kinds of proteins. For example, the combinatorial large number of possible sequences and the incomplete understanding of the factors that control protein structure are still the primary obstacles in protein design. The Examples clearly illustrate the need to impose restrictions for the successful design of the secondary structure of the enzyme protein. Amino acid residues

Art Unit: 1627

are selected such that cys is not used to prevent disulfide formation or Gly that can compromise flexibility and Pro for which a appropriate rotamer is difficult to define. Note further the restriction in the computer design using known primary structure of the known enzyme as obtained from the Protein Data Bank wherein water and SO₂ have been deleted to remove any obstacles for its successful design. Therefore, the broad claimed method drawn to any type of protein simply utilizing the force field calculation that results in a secondary structure for any or all type of proteins requires an undue amount of experimentation. While computer protein design holds no barrier or limit, but ultimately the question that needs to be asked, is if such design is feasible in the actual environment where the protein exists. The broad claimed method steps containing too numerous unknown variables are nothing more than an invitation to experiment.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35

U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Art Unit: 1627

Claims 12-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A). Claims 12 and 16 are incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps by which the mere use of a force field calculation produces a probability distribution table of amino acid residues in a plurality of variant positions. And, the combining of the probability distribution of amino acids that results in a secondary sequence. It is not clear whether the plurality of variant positions of the residue is relative to a peptide sequence and if so, how the table of amino acid residues is distributed along the peptide sequence by the mere use of force field calculation. Thus, there seems to be no nexus between the two steps as some steps there between are missing. It is not clear how the distribution of amino acid residues in a table is effected to be a probability residue as it is not clear as to what constitutes a table and/or the kind and number of residues contained therein. The term "probability" fails to ascertain the claimed

Art Unit: 1627

invention with precision, it connotes uncertainty rendering the claim indefinite.

The preamble recites for "generating a secondary library of scaffold protein variants" while the body of the claim, recites for "a secondary library of secondary sequences". Also, step b) recites a "secondary library of secondary sequences" while the concluding claim recites "secondary variants". It is not clear whether the scaffold protein variants in the preamble are the same as the secondary sequences in the body of the claims. The use of inconsistent terminologies provide for confusion and ambiguity. The terms "primary and secondary variants" in claims 12 and 16 and "tertiary" in claim 14 are relative terms, which render the claims indefinite. The terms "primary and secondary" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear as to the relative or arbitrary designation of said primary and secondary sequences. The metes and bound of the terms "protein variants", "primary variants" and "plurality" are not clearly set forth in the claims. There is lack of antecedent basis of support for the "said primary variants".

Art Unit: 1627

B). The use of abbreviation, SCMF is ambiguous. It is suggested that applicants provide for the full name of the abbreviation. Claim 13.

C). Claims 14 and 15 do not add further limitation to the base claim. It broadens the base in claim in that these claims recite for the use of computer program. The use of the trademark PDA in the claim is indefinite, uncertain, and arbitrary. The characteristics of the product (herein, program) may change from time to time and yet it may continue to be sold under the same trademark. In patent specifications, every element or ingredient of the product should be set forth in positive, exact, intelligible language, so that there will be no uncertainty as to what is meant. Arbitrary trademarks, which are liable to mean different things at the pleasure of manufacturers, do not constitute such language. Ex Parte Kattwinkle, 12 USPQ 11 (Bd. App. 1931). See also, MPEP 608.01(v). This rejection has similar import on claims 17 and 18.

D). Claim 16 is indefinite as to the use of alignment **program**. See C) rejection above. Further, it is not clear, within the claimed context, the computational ranking of said secondary library.

E). Claims 19 and 20 are indefinite as to the difference between a sequence and structural alignment program, within the

Art Unit: 1627

claimed context, especially in the absence of positive showing in the specification.

F). Claims 21-25 do not further limit the base claim 12 or 16. Each of the base claims recites generating secondary library of **protein** variants sequences using computer method. Claims 21-23 relate to synthesis of oligonucleotide, not proteins. Therefore, these claims are broadening the base claim and lack antecedent basis of support. Furthermore, the terms "relative" amounts (claim 25) and "equimolar amounts" are indefinite as the metes and bounds of these amounts are not clearly set forth in the specification or claims. Also, it is not clear as to the amounts that "correspond" to the frequency of mutation. Claim 24.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Art Unit: 1627

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,22 of U.S. Patent No. 6,269,312 ([312 Patnet (1)] or claims 1-8 of U.S. Patent No. 6,403,312 ['312(11)]. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claimed method uses the same PDA program as each of the '312 Patents except the instant method uses an alignment program. However, the disclosure of the '312 Patent(1) discloses said alignment program at col. 3, line 51.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Dahiyat et al (Protein Science).

Dahiyat discloses at page 896 a method by which a protein variants are made by protein design automation(PDA) to create a secondary library of protein variant sequences (rotamers). Dahiyat further discloses that the side chains are described by

Art Unit: 1627

rotamers and an atomistic force field is used to score rotamer arrangements. The conformationally site (rotamers) was varied that results in a protein having a secondary sequences different from the primary sequence from which the secondary sequences (containing a library of rotamers) are obtained. Accordingly, the specific process steps of Dahiyat using force field to score rotamer arrangement (probability distribution table of residues, as claimed) fully meet the broad claimed process step.

Claims 16-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Dahiyat et al (Science).

Dahiyat discloses a method of generating a secondary protein variants comprising designing by protein design automation the secondary structure (rotamers) of beta beta alpha motif of the zinc finger DNA binding module. An alignment of the modified structure of the Zif268, page 83, col. 3 is then made using BLAST program. Dahiyat's disclosure of generating a secondary structure for a zinc finger protein using alignment algorithm as BLAST fully meets the broad claimed process steps.

Claims 1-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Mayo et al (WO 98/47089).

Mayo basically discloses the same method steps as each of the Dahiyat references, above. See e.g., page 15, lines 4-7; page 46, line 34 up to page 47, line 10 for the use of force

Art Unit: 1627

field calculation in generating a secondary structures for protein variants (rotamers) and page69, Example 5 for the use of alignment, specifically Fig. 11, page 71.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mayo in view of applicants' disclosure of known prior art.

Mayo does not disclose the synthesis of the protein or the nucleotides that would perhaps encode the protein (as best as the claimed can be interpreted). However, applicants admit at page 40, line 21 and lines 25-35 that "...[DNA] shuffling, as is generally known in the art, can be done with multiple libraries.....[error-prone PCR], for example using modified nucleotides; known mutagenesis technique." Accordingly, it would have been obvious to one having ordinary skill in the art at the

Art Unit: 1627

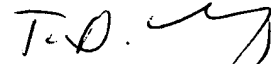
time the invention was known to synthesize the modified sequences of Mayo using PCR methodology since this DNA method of synthesis is well known in the art of oligo synthesis as admitted by applicants in the disclosure.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (703) 308-3967. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-7924 for regular communications and (703) 308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


T. D. Wessendorf
Primary Examiner
Art Unit 1627

tdw
September 27, 2002